



Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2

by Paul M. Barr, Tadeusz Robak, Carolyn Owen, Alessandra Tedeschi, Osnat Bairey, Nancy L. Bartlett, Jan A. Burger, Peter Hillmen, Steven Coutre, Stephen Devereux, Sebastian Grosicki, Helen McCarthy, Jianyong Li, David Simpson, Fritz Offner, Carol Moreno, Cathy Zhou, Lori Styles, Danelle James, Thomas J. Kipps, and Paolo Ghia

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Title: Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2

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Summary (2 sentences to summarize the work that is used for journal's facebook page)

An extended analysis of RESONATE-2 demonstrates that first-line treatment with ibrutinib provides sustained progression-free survival benefits, with depth of response improving over time without unexpected toxicity concerns in older patients with chronic lymphocytic leukemia. Additionally, ibrutinib overcomes the adverse prognostic impact of del (11q) and unmutated *IGHV* status.

Trial registration: ClinicalTrials.gov identifiers: NCT01722487 and NCT01724346

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Abstract (250-word limit; single paragraph only): 250

Results of RESONATE-2 (PCYC-1115/1116) supported approval of ibrutinib for first-line treatment of chronic lymphocytic leukemia. Extended analysis of RESONATE-2 was conducted to determine long-term efficacy and safety of ibrutinib in older patients with chronic lymphocytic leukemia. A total of 269 patients aged ≥ 65 years with previously untreated chronic lymphocytic leukemia without del(17p) were randomized 1:1 to ibrutinib (n=136) or chlorambucil (n=133) on days 1 and 15 of a 28-day cycle for 12 cycles. Median ibrutinib treatment duration was 28.5 months. Ibrutinib significantly prolonged progression-free survival versus chlorambucil (median, not reached vs 15 months; hazard ratio, 0.12; 95% confidence interval, 0.07-0.20; $P < .0001$). The 24-month progression-free survival was 89% with ibrutinib (97% and 89% in patients with del[11q] and unmutated immunoglobulin heavy chain variable region gene, respectively). Progression-free survival rates at 24 months were also similar regardless of age (< 75 years [88%], ≥ 75 years [89%]). Overall response rate was 92% (125/136). Rate of complete response increased substantially from 7% at 12 months to 18% with extended follow-up. Greater quality of life improvements occurred with ibrutinib versus chlorambucil in Functional Assessment of Chronic Illness Therapy-Fatigue ($P = .0013$). The most frequent grade ≥ 3 adverse events were neutropenia (12%), anemia (7%), and hypertension (5%). Rate of discontinuations due to adverse events was 12%. Results demonstrated that first-line ibrutinib for elderly patients with chronic lymphocytic leukemia provides sustained response and progression-free survival benefits over chemotherapy with depth of response improving over time without new toxicity concerns. This trial was registered at clinicaltrials.gov ([NCT01722487](https://clinicaltrials.gov/ct2/show/study/NCT01722487) and [NCT01724346](https://clinicaltrials.gov/ct2/show/study/NCT01724346)).

Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in Western countries and is increasing in prevalence with the prolonged survival observed with introduction of novel combinations and targeted treatments such as ibrutinib.¹ With a median age at diagnosis of 71 years,¹ management of this predominately older population is controversial given that frequent comorbidities often preclude aggressive therapy. Randomized studies have provided disparate results in older compared with younger patients.^{2,3} Less intensive approaches, such as chlorambucil, provide limited response durability. While the addition of anti-CD20 antibodies has improved outcomes achieved with single-agent chlorambucil, administration of these intravenous agents has associated toxicity, and response durations remain limited.⁴

The first-in-class, oral, once-daily, Bruton's tyrosine kinase (BTK) inhibitor ibrutinib targets signaling via the B-cell receptor cascade, critical to survival of malignant lymphocytes.⁵⁻⁹ Ibrutinib demonstrated tolerability, a high rate of objective responses, and prolongation of progression-free survival and overall survival in patients with relapsed/refractory CLL.¹⁰ Early-phase studies demonstrated responses of up to 84% in previously untreated patients with complete response (CR) rates of up to 23% and up to 3 years of median follow-up.^{11,12} This small cohort suggested that single-agent ibrutinib might provide durable efficacy in first-line treatment of patients with CLL while avoiding toxicity inherent to cytotoxic or other infused regimens.

RESONATE-2, was an international phase 3 study designed to definitively evaluate first-line ibrutinib treatment in older patients who often had baseline frailties against a standard chemotherapeutic agent, chlorambucil.¹³ Primary results demonstrated an 84% reduction in the risk of death at a median follow-up of 18 months for ibrutinib compared with chlorambucil. Based on these findings, ibrutinib received approval in the United States, Europe, and other regions for the first-line treatment of patients with CLL, and allows for treatment without chemotherapy.^{14,15} A detailed analysis of overall survival (OS) with longer follow-up and adjustment for the impact of treatment crossover was previously reported.¹⁶ A separate data cut was subsequently performed after this detailed OS analysis to evaluate additional outcomes after long-term follow-up. Herein, we present the extended analysis of additional outcomes from RESONATE-2 including quality-of-life (QOL) measures that may help guide appropriate use of ibrutinib for previously untreated patients.

Methods

Study design and population

Eligible patients for RESONATE-2 (PCYC-1115/1116; [NCT01722487/NCT01724346](#)) had previously untreated CLL or SLL with active disease and were ≥ 65 years. Patients ≤ 70 years of age must have had a comorbidity that precluded treatment with fludarabine-cyclophosphamide-rituximab. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , absolute neutrophil count ≥ 1000 cells/mm³, platelet count $\geq 50,000$ /mm³, and adequate liver and kidney function. Those with del(17p) CLL were excluded.

This study was conducted according to principles of the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice and approved by the institutional review boards of participating institutions. All patients provided written informed consent.

Patients were randomly assigned in a 1:1 ratio to treatment with oral ibrutinib, 420 mg once daily until disease progression or chlorambucil, 0.5 mg/kg (increased up to 0.8 mg/kg based on tolerability) on days 1 and 15 of a 28-day cycle for 12 cycles. Patients from the chlorambucil treatment arm with independent review committee (IRC)-confirmed disease progression were eligible to cross over to second-line treatment with ibrutinib at the investigator's discretion.

End points and assessments

End points included progression-free survival (PFS, defined as time from randomization to progression or death, whichever occurs earlier), overall survival (OS), overall response rate (ORR), improvement in hematologic variables, patient-reported health-related QOL, and safety. Disease progression and response was determined by investigator. QOL was assessed using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue questionnaires. Safety assessments included adverse events (AEs) and laboratory parameters. Nonhematologic AEs were graded using Common Terminology Criteria for Adverse Events, v4.03. Hematologic AEs were graded using International Workshop on CLL criteria.¹⁷

Statistical analyses

PFS and OS were analyzed using Kaplan-Meier estimates and a 2-sided log-rank test stratified by the randomization factors. Sensitivity analyses were performed to adjust for the impact of crossover on OS as previously described.¹⁶ ORR was analyzed with the Cochran-Mantel-Haenszel chi-square test, stratified by the randomization factors. QOL analyses were based on the proportion of patients with clinically meaningful changes in scores from baseline (≥ 3 points for FACIT-Fatigue). Additional QOL analyses used time-dependent mixed-models repeated measures analysis.

Results

Patients

There were 269 patients randomly assigned to ibrutinib (n=136) or chlorambucil (n=133) monotherapy in the RESONATE-2 study (**Figure S1**).¹³ Patient characteristics were well balanced across treatment arms, as previously reported (**Table 1**).¹³ The median patient age was 73 years on the ibrutinib arm and 72 years on the chlorambucil arm. In the ibrutinib treatment arm, of those evaluated, 22% (29/130) had del(11q), and 48% (58/121) had unmutated *IGHV*. Patients initiated ibrutinib treatment for active disease per iwCLL criteria, most commonly manifesting as marrow failure (progressive anemia or thrombocytopenia [40%]), progressive or symptomatic lymphadenopathy (40%) or splenomegaly (26%), with many patients having more than one indication for treatment including disease symptoms such as fatigue or night sweats (Table 1). Although 32% of patients had substantial fatigue when entering study, only 5% were started on CLL

treatment solely for fatigue that was considered to have interfered with work or usual activities. With a median follow-up for this extended analysis of 29 months (maximum, 36 months), 107 patients (79%) remain on first-line ibrutinib.

Survival outcomes

Ibrutinib resulted in significantly longer PFS compared with chlorambucil (median, PFS not reached vs 15.0 months; **Figure 1A**). There was an 88% reduction in risk of PFS events (progression or death; hazard ratio [HR], 0.12; 95% CI, 0.07-0.20; $P < .0001$) for patients randomized to ibrutinib. PFS at 24 months was 89% with ibrutinib versus 34% with chlorambucil. This rate was relatively stable with ibrutinib with an 18-month PFS of 94%. Ibrutinib consistently demonstrated significant improvements in PFS for patients in all subgroups including those considered high risk (**Figure 2**). In patients treated with ibrutinib, only 1 patient with del(11q) has had disease progression and the rates of 24-month PFS were 97% and 86% for those with or without del(11q), respectively (**Figure 1B**). No significant difference was observed in the PFS of patients with unmutated versus mutated *IGHV* (24-month PFS, 90% and 89%, respectively; **Figure 1C**). PFS benefits were consistent across additional subgroups of patients, including those with advanced disease (Rai stage 3 or 4) or bulky disease (**Figure 2**). PFS and OS rates were also similar regardless of age (24-month PFS, <75 years [88%], ≥75 years [89%]; OS, <75 years [94%], ≥75 years [96%]; **Figure S2**). With longer follow-up and despite patient crossover, ibrutinib continues to demonstrate an OS benefit compared with chlorambucil (HR, 0.43; 95% CI, 0.21-0.86; $P=.0145$; **Figure S3 and Table S1**), with a 24-month OS of 95% for ibrutinib vs. 84% for chlorambucil (**Figure S3**).

Responses for ibrutinib-treated patients

With a maximum of 36 months of follow-up, the ORR with ibrutinib treatment was 92% (**Table 2**). Eighteen percent of patients achieved CR, which improved from 7% at 12 months and 15% at 24 months (**Figure 3**). Comparable ORR and CR rates were also observed in high-risk subgroups, including those with del(11q) (ORR, 100%; CR rate, 14%) or unmutated *IGHV* (ORR, 95%; CR rate, 21%).

Disease burden and symptoms

The vast majority of ibrutinib-treated patients experienced substantial reduction in lymphadenopathy and splenomegaly at the time of the primary analysis which was much greater than observed with chlorambucil. A $\geq 50\%$ reduction in the lymph node sum of the product of longest diameter (SPD) occurred in 95% of patients treated with ibrutinib versus 40% of those treated with chlorambucil, with complete resolution in lymphadenopathy in 42% versus 7%, respectively (**Figure S4A, B**). Reduction in splenomegaly by $\geq 50\%$ occurred in 95% with ibrutinib versus 52% with chlorambucil, with complete resolution in splenomegaly in 56% versus 22%, respectively (**Figure S4C, D**). Ibrutinib also resulted in higher rates of improvements in disease symptoms including weight loss, fatigue, and night sweats, which were indications for therapy in many patients.

Patient-reported QOL

Greater improvements in QOL occurred with ibrutinib versus chlorambucil in FACIT-Fatigue ($P=.0013$) by repeated measure analyses (**Figure S5**). Clinically meaningful improvements occurred more frequently with ibrutinib versus chlorambucil in FACIT-Fatigue, although this was not statistically significant (86/136 [63%] vs 71/133 [53%]; odds ratio, 1.50; 95% CI, 0.92-2.45; $P=.1013$).

Safety and tolerability of ibrutinib

Median treatment duration with ibrutinib was 28.5 months (range, 0.7-35.9 months). Most patients continue ibrutinib treatment, with 83% (112/135) receiving ibrutinib continuously for durations exceeding 2 years. The most frequent AEs with ibrutinib with extended follow-up were similar to the primary report¹³: diarrhea, fatigue, cough, anemia, and nausea (**Table S2**). Grade ≥ 3 AEs were generally observed more frequently during the first 12 months of ibrutinib therapy and generally decreased over time (**Figure 4**). Rates of grade ≥ 3 cytopenias decreased over time from 8.1%, 5.9%, and 2.2% during the first year of treatment to 0%, 1%, and 0% during the third year of treatment for neutropenia, anemia, and thrombocytopenia, respectively.

Several AEs of clinical interest were characterized in greater detail (**Table 3**). Diarrhea generally occurred early in treatment (median, 26 days) and was completely reversible in 95% of patients within a median of 6 days. Visual disturbances (blurred vision or reduced visual acuity) were grade 1 or 2, with 57% of these completely resolving within a median of 37.5 days after onset. Hypertension occurred at a median of 187 days, with

improvements reported at a median of 14 days after onset. Arthralgia was observed at a median of 135 days and was generally reversible (78% complete, 4% partial) within a median duration of approximately 3 weeks. Atrial fibrillation was observed throughout treatment follow-up, with 4% of patients experiencing a grade 3 event. Symptoms of atrial fibrillation quickly resolved in the majority of patients (57% complete, 7% partial resolution) within a median of 3 days. Nine patients (7%) experienced a major hemorrhage occurring at a median of 310 days. Of these, 3 patients were reported to have active treatment with concomitant medications that impact platelets or coagulation (aspirin, low molecular weight heparin, and naproxen respectively) including a traumatic hematoma, post-procedural hematoma, and hematuria, all of which were grade 3 in severity and did not result in study drug discontinuation. Grade ≥ 3 infection occurred in 23% of patients at a median of 138 days, including 2 that were fatal (Klebsiella infection and septic shock). Grade ≥ 3 infections were observed most frequently in the first year of treatment and decreased thereafter (**Figure 4**). There were no cases of pneumocystis pneumonia or multifocal leukoencephalopathy reported.

Serious AEs over the 3 years of follow-up occurring in more than 2 ibrutinib-treated patients, included pneumonia (11; 8%), atrial fibrillation (6; 4%), urinary tract infection (5; 4%), basal cell carcinoma (5; 4%), hyponatremia (5; 4%), pleural effusion (4; 3%), hypertension (3; 2%), and anemia (3; 2%).

Eighteen patients (13%) required dose reductions and 16 patients (12%) discontinued first-line ibrutinib because of AEs. AEs leading to discontinuation in more than 1 patient included infection (n=5), hemorrhage (n=3), atrial fibrillation (n=2), and rash (n=2). Treatment-limiting toxicity including both reductions and discontinuations due to AEs decreased over time with ibrutinib (**Figure 4**).

Concomitant medications

Concomitant medications were collected throughout the duration of ibrutinib treatment (median, 28.5 months) and chlorambucil (median, 7.1 months). Despite longer follow-up recording of the use of these agents in the ibrutinib arm versus the chlorambucil arm, the rate of neutrophil growth factor use and platelet and red blood cell transfusion was higher in the chlorambucil arm. Intravenous immunoglobulin was administered to 4% of ibrutinib-treated patients versus 2% of those randomized to chlorambucil.

Anticoagulants and/or antiplatelet agents were frequently used during study therapy (56% and 54% of patients treated with ibrutinib and chlorambucil, respectively; **Table S3**), including anticoagulants in 21% of the ibrutinib-treated patients.

Outcomes following ibrutinib discontinuation

With up to 3 years follow-up, out of 136 patients, only 4 patients discontinued ibrutinib primarily due to disease progression; 1 had unmutated *IGHV* and none were reported to have del(11q). Two of these 4 patients remain alive. Of the 16 patients who discontinued ibrutinib because of AEs; 13 (81%) are alive with a median of 13 months follow-up after ibrutinib discontinuation and 3 have died (**Table S4**). Ten of the patients

had PR as best response, 4 patients discontinued after not responding to ibrutinib and 2 patients discontinued prior to response evaluation. Non-responders/non-evaluable had a PFS that ranged from 1.8 to 20.2 months, while responders tended to have a variable but longer PFS (4.2–34.0 months). As the vast majority of patients (79%) remain on single-agent ibrutinib, this analysis is limited in size and also to the patients who came off treatment fairly early (9 of the 16 patients who discontinued due to AEs did so in the first year). In total 7 patients received subsequent therapy after ibrutinib at a median of 7.6 months following ibrutinib discontinuation (range, 1.2 to 20.8 months), including fludarabine-cyclophosphamide-rituximab (n=3), bendamustine-rituximab (n=2), chlorambucil (n=1), and radiation (n=1). Six of these 7 patients (86%) remain alive with median follow-up of 21 months (range, 9 to 25 months).

Discussion

This extended analysis of RESONATE-2 with detailed clinical follow-up demonstrates that ibrutinib continues to provide significant and sustained clinical benefits, improving the quality of responses, for the first-line treatment of older patients with CLL or SLL with a manageable safety profile over extended durations of treatment. Consistent with the initial report, ibrutinib demonstrates a significant 88% reduction in the risk of PFS events (progression or death) compared with chlorambucil ($P < .0001$) with extended follow-up. In addition, the OS benefit for ibrutinib compared with chlorambucil was maintained, despite crossover to treatment with ibrutinib for many patients in the chlorambucil arm (n=55). These data support the use of ibrutinib in the first-line treatment of CLL as a chemotherapy-free option that can be taken continuously

achieving long term disease control for the majority of patients including those with high risk features.^{10,13} Ibrutinib has a category 1 National Comprehensive Cancer Network[®] (NCCN[®]) recommendation as a single-agent first-line treatment for CLL without del(17p) in patients ≥65 years and for relapsed/refractory CLL without del(17p).¹⁸

The efficacy of ibrutinib in the first-line setting appears superior to that observed in relapsed or refractory patients.¹⁹ Nearly all patients randomly assigned to ibrutinib achieved rapid disease reduction, with an ORR of 92% translating to high rates of 24-month PFS and OS of 89% and 95%, respectively, with similar PFS and OS rates seen regardless of age. This observation suggests that ibrutinib may be most effective when used upfront before the acquisition of poor-risk molecular aberrations, which are selected for with chemotherapy.^{20,21} Additionally, sensitivity analyses to adjust for the effects of patients in RESONATE-2 who crossed over to ibrutinib found that treatment with ibrutinib was still associated with statically significant OS compared with chlorambucil.¹⁷ These results also demonstrate that depth of response substantially increases over time, with higher rates of CR during the extended follow-up, indicating a persistent action of the drug rather than a simple maintenance effect. Similar findings were observed with long-term follow-up of patients enrolled in the phase 2 trial of first-line ibrutinib.¹¹ Within this previous study, 29% of patients achieved a CR, and 92% remained alive and progression free at 5 years.²² Given this data, the CR rate will likely continue to increase in the present study as long-term disease control and high tolerability with first-line use can be expected based on the earlier phase 2 results.¹²

In addition to the efficacy benefits overall, sustained robust outcomes were demonstrated in higher-risk groups. No difference in outcome was observed in patients with unmutated *IGHV* status, a traditional poor prognostic indicator for all chemoimmunotherapy regimens. Notably the rate of unmutated *IGHV* in this study of older patients was somewhat lower than other studies at 48% (vs. 58%-62% in CLL11), consistent with prior reports of higher frequency of unmutated *IGHV* in younger patients.^{4,23} For patients with del(11q), another traditionally high-risk subgroup, 100% of the 29 patients responded to treatment with ibrutinib, and there was a 99% reduction in the risk of progression or death, with only 1 del(11q) ibrutinib-treated patient experiencing disease progression after discontinuing therapy for AE over the extended follow-up. While this represents a relatively small patient subset (22%), ibrutinib demonstrates a particularly significant benefit in this population, which historically experiences inferior outcomes with traditional chemotherapy or CD20-based regimens.²⁴⁻²⁶ Combined analysis of 3 randomized studies not only demonstrated superiority of ibrutinib over traditional chemotherapy and/or anti-CD20 comparators for patients with del(11q), but also equally positive PFS and OS outcomes irrespective of del(11q). These results suggest that current definitions of high-risk disease and the impact of prognostic biomarkers may need to be redefined with ibrutinib.²⁷ The mechanism why del(11q) patients may have better outcomes when treated with ibrutinib is of high interest and is the subject of ongoing research.

Safety of therapy administered to older patients over the long term is an area that requires close scrutiny. First-line ibrutinib appears to be well tolerated with extended

treatment as evidenced by over 80% of this older population being able to continue treatment for more than 2 years. This extended follow-up allowed for new observations into the timing of when AEs occurred and time to resolution of AEs as well as the use of transfusions and growth factors. Diarrhea, while frequent, often occurred early during the first several months of treatment and was generally low grade and short lived. Severe and treatment-limiting AE rates decreased over time with extended ibrutinib treatment. A decrease in myelotoxicity and infectious complications over time was also observed. This contrasts with chemoimmunotherapy-associated AEs and was importantly associated with less medical resource utilization of neutrophil growth factors and slightly less transfusion need despite 4 times the treatment time with ibrutinib. While the rate of atrial fibrillation increased from 6% in the primary analysis¹³ to 10%, overall, ibrutinib dose reduction or discontinuation due to atrial fibrillation was uncommon and lessened with extended treatment in this population of older patients with CLL. Atrial fibrillation therefore appears manageable and does not frequently necessitate ibrutinib discontinuation. Additional information on the management and outcomes of atrial fibrillation along with associated anticoagulant therapy has been provided in a large pooled analysis of ibrutinib studies.²⁸ Rates of major hemorrhage remained low despite half the patients receiving concomitant antiplatelet or anticoagulant medications.

Previous work demonstrated that QOL is significantly compromised in patients with CLL, affecting physical fitness, cognitive function, levels of fatigue, and sleep. Worse scores were reported for patients receiving chemotherapy such as chlorambucil.²⁹ Even with the addition of contemporary anti-CD20 agents (obinutuzumab), no significant benefit in

QOL has been noted.⁴ However, this extended follow-up provides the first analysis of QOL, as measured by FACIT Fatigue Scale, following ibrutinib treatment in previously untreated patients. Significantly greater improvements in QOL were observed with ibrutinib versus chlorambucil. In line with this and the favorable impact on QOL and tolerable safety profile, 79% of patients remained on first-line treatment with ibrutinib at the time of this later analysis with up to 3 years of therapy.

Patients who discontinue treatment for CLL including ibrutinib may have varied outcomes dependent on the reason for discontinuation.³⁰ In 1 study that included mostly patients with relapsed or refractory CLL, median OS following ibrutinib therapy was 33 months for those who discontinued because of AEs versus 16 months for those who discontinued because of disease progression. In our study, the 22 patients who discontinued therapy had a median follow-up of 13 months after discontinuation. Of these 22 patients, 16 are still alive, while 2 of the 4 patients who progressed have died. Seven patients have received subsequent treatment, mostly chemoimmunotherapy (BR, FCR); 6 of those patients are still alive with a median of 21 months of follow-up. While retrospective analyses of real-world data have previously suggested that treatment with an alternate kinase inhibitor is more effective than chemoimmunotherapy following discontinuation of ibrutinib,^{31,32} our data suggests that patients who discontinue ibrutinib can respond to chemoimmunotherapy as second line therapy. Continued follow-up of patients in the RESONATE-2 trial who have discontinued ibrutinib will provide the needed further data as relatively few patients have progressed or stopped therapy to date.

These data confirm that first-line treatment with ibrutinib results in long-term PFS in patients with CLL and that response quality continues to improve with ibrutinib over time with substantial increased in patients achieving CR. In addition, rates of grade ≥ 3 AEs during treatment with ibrutinib decreased over time. The most common reasons for initiating first-line treatment in these patients, including marrow failure, disease burden, and disease symptoms, all improved to greater extents in patients treated with ibrutinib versus chemotherapy. Ongoing randomized studies, including ILLUMINATE (NCT02264574), comparing ibrutinib-obinutuzumab with chlorambucil-obinutuzumab, and A041202 (NCT01886872), comparing ibrutinib, ibrutinib-rituximab, and rituximab-bendamustine, will continue to define the role of ibrutinib for the first-line treatment of patients with CLL/SLL.

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Authorship

Contribution: C.Z., L.S., and D.J. designed the study. P.M.B., C.O., A.T., O.B., N.B., J.A.B, P.H., S.C., S.D., S.G., H.M, J.L., D.S., F.O., C.M., T.J.K, and P.G. contributed to collecting the data with the other RESONATE-2 investigators and their research teams. All authors had full access to the data, were involved in data interpretation, and vouch for accuracy of the data. P.M.B., C.Z., L.S., and D.J. collaboratively wrote the first draft of the manuscript. All authors reviewed and revised the manuscript, provided final approval, and made the decision to submit the manuscript for publication. Medical writing support was provided by a professional medical writer and funded by the sponsor.

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consultancy/advisory role, and speakers' bureau for AbbVie, Janssen, Gilead, and Acerta; and research funding from AbbVie, Pharmacyclics LLC, an AbbVie Company, Janssen, Roche, GlaxoSmithKline, and Gilead. Dr Coutre reported a consultancy/advisory role for AbbVie, Gilead, Novartis, Celgene, Janssen, and Pharmacyclics LLC, an AbbVie Company; and research funding from AbbVie, Pharmacyclics LLC, an AbbVie Company, Gilead, Celgene, and Novartis. Dr Devereux reported honoraria and a consultancy/advisory role for Janssen, AbbVie, MSD, and Gilead; and speakers' bureau and travel expenses for Janssen and Gilead. Dr McCarthy reported honoraria and travel expenses from Roche, AbbVie, Novartis, and Janssen; and a consultancy/advisory role with Janssen. Dr Simpson reported honoraria from Roche, Janssen, Merck, and Celgene; and research funding from Amgen. Dr Moreno reported a consulting/advisory role with Janssen, AbbVie and Gilead; and research funding from Gilead and Roche. Cathy Zhou and Dr Styles reported employment and travel accommodations from Pharmacyclics LLC, an AbbVie Company, and stock ownership with AbbVie. Dr James reported employment with Pharmacyclics LLC, an AbbVie Company; spouse employment with AbbVie; stock ownership for self/husband with AbbVie; and patents/royalties/other intellectual property with AbbVie. Dr Kipps reported a consultancy/advisory role for AbbVie, Genentech, Gilead, Pharmacyclics LLC, an AbbVie company and Celgene; and research funding from AbbVie, Genentech, Roche, Pharmacyclics LLC, an AbbVie Company, and Oncternal. Dr Ghia reported a consultancy/advisory role for AbbVie, Adaptive, Gilead, Janssen, Pharmacyclics LLC, an AbbVie Company, and Roche; research funding from

AbbVie, Gilead, Janssen, and Novartis; and speakers' bureau for Gilead. Dr Offner, Dr Grosicki and Dr Li reported no relevant financial disclosures.

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Tables

Table 1. RESONATE-2 Reasons for Initiation of Treatment and Baseline Patient Characteristics¹

	Ibrutinib (n=136)	Chlorambucil (n=133)
Baseline Characteristic		
Median age (range), y	73 (65-89)	72 (65-90)
≥ 75 y, (%)	46 (34)	47 (35)
Male, n (%)	88 (65)	81 (61)
ECOG performance status, n (%)		
0	60 (44)	54 (41)
1	65 (48)	67 (50)
2	11 (8)	12 (9)
Rai stage III or IV, n (%)	60 (44)	62 (47)
Bulky disease ≥ 5 cm, n (%)	54 (40)	40 (30)
Hierarchical Classification ^a , n (%)		
Del(11q)	29/130 (22)	25/121 (21)
Trisomy 12	20/117 (17)	23/108 (21)
Del(13q)	25/112 (22)	32/108 (30)
None of above	38/112 (34)	28/108 (26)
<i>IGHV</i> status ^b , n/N (%)		
Mutated	40/121 (33)	42/127 (33)
Unmutated	58/121 (48)	60/127 (47)
Unclassifiable ^c	23/121 (19)	25/127 (20)
Patients meeting criteria for active disease, n (%)		
Progressive marrow failure	54 (40)	49 (37)
Lymphadenopathy	55 (40)	44 (33)
Splenomegaly	36 (26)	44 (33)
Progressive lymphocytosis	23 (17)	28 (21)
Autoimmune anemia and/or thrombocytopenia	3 (2)	5 (4)
Any documented constitutional symptoms	64 (47)	56 (42)
Unintentional weight loss (>10% within 6 months)	14 (10)	16 (12)
Significant fatigue	44 (32)	29 (22)
Fever	4 (3)	3 (2)
Night sweats	32 (24)	35 (26)

ECOG, Eastern Cooperative Oncology Group. FISH denotes fluorescence in situ hybridization, and *IGHV* the immunoglobulin heavy-chain variable-region gene

^aPatients with missing results were excluded (Del(11): n=6 for ibrutinib, n=12 for chlorambucil; Trisomy 12: n=19 for ibrutinib, n=25 for chlorambucil; Del(13q): n=24 for ibrutinib, n=25 for chlorambucil; None of the above: n=24 for ibrutinib, n=25 for chlorambucil).

^bPatients with missing results were excluded (n=15 for ibrutinib, n=6 for chlorambucil).

^cUnclassifiable includes patients with polyclonal *IGHV* status if no specific *IGHV* subfamily member was dominant (>50% of all reads) and samples with no amplification.

Table 2. Response rates in ibrutinib-treated patients

Best response, n (%)	Ibrutinib-treated patients				
	All patients (n=136)	With del(11q) (n=29)	Without del(11q) (n=101)	Mutated <i>IGHV</i> (n=40)	Unmutated <i>IGHV</i> (n=58)
ORR	125 (92)	29 (100)	91 (90)	35 (88)	55 (95)
CR/CRi	25 (18)	4 (14)	20 (20)	8 (20)	12 (21)
nPR	1 (1)	0	1 (1)	3 (8)	0
PR	97 (71)	25 (86)	68 (67)	26 (65)	43 (74)
PR-L	2 (1)	0	2 (2)	0	0

CRi, complete response with incomplete blood-count recovery; nPR, nodular partial response (defined according to the International Workshop on Chronic Lymphocytic Leukemia criteria for response¹⁶ as a complete response with lymphoid nodules in the bone marrow); PR, partial response; PR-L, partial response with lymphocytosis.

Table 3. Characterization of select AEs of clinical interest in ibrutinib-treated patients observed at any time during follow-up^a

AE	Ibrutinib-treated patients n=135 n (%)					Resolution, n (%)		Median time to first event, days					Median time from onset to resolution/ improvement, days			
Grade	Any	2	3	4	5	Complete	Partial	Any	2	3	4	5	Any	2	3	4
Diarrhea	61 (45)	16 (12)	5 (4)	0	0	58 (95)	0	26	131	219	NA	NA	6	3	6.5	NA
Visual disturbances ^b	30 (22)	6 (4)	0	0	0	17 (57)	0	100	201	NA	NA	NA	37.5	74.5	NA	NA
Hypertension ^c	27 (20)	13 (10)	7 (5)	0	0	12 (44)	1 (4)	187	187	109.5	NA	NA	14	36	9	NA
Arthralgia	27 (20)	9 (7)	3 (2)	0	0	21 (78)	1 (4)	135	55	135	NA	NA	22	22	15	NA
Atrial fibrillation	14 (10)	7 (5)	6 (4)	0	0	8 (57)	1 (7)	249.5	85	773.5	NA	NA	3	2	7	NA
Major hemorrhage	9 (7)	1 (< 1)	7 (5)	1 (1)	0	9 (100)	0	310	155	446	254	NA	13.5	14.0	11.0	45.0
Infections (grade ≥ 3)	31 (23)	NA	28 (21)	4 (3)	2 (1)	28 (90)	0	138	NA	119	367.5	422	9	NA	9	16

AE, adverse event; NA, not applicable.

^aFrom first dose of study treatment up to 30 days after last dose or initiation of subsequent anti-cancer therapy, whichever occurs earlier

^bVisual disturbances included the preferred terms blurred vision and reduced visual acuity

^cHypertension (standardized MEDRA queries) group of preferred terms.

Figure Legends

Figure 1. PFS for the intent-to-treat population. Survival analyses from randomization until event or censored at last follow-up using the Kaplan-Meier method. Vertical ticks indicate censored patients.

PFS, progression-free survival.

Figure 2. PFS subgroup analysis.

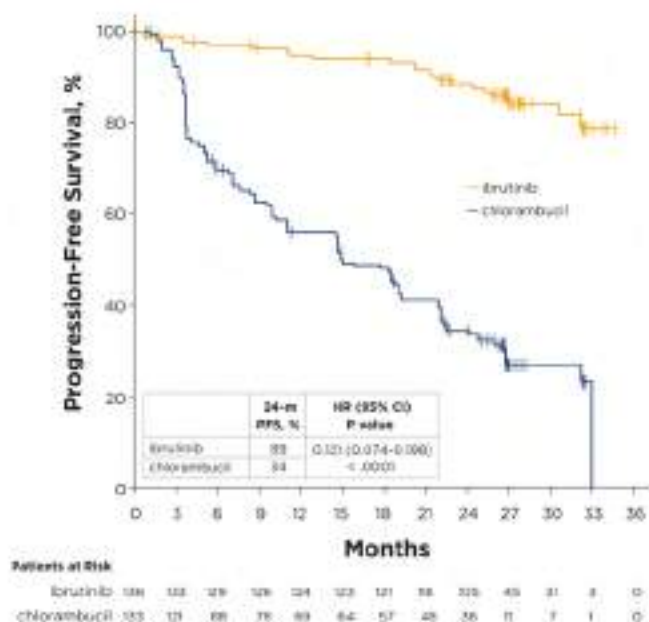
Figure 3. Response rates over time in ibrutinib-treated patients.

CR, complete response; CRi, complete response with incomplete blood-count recovery; nPR, nodular partial response (defined according to the International Workshop on Chronic Lymphocytic Leukemia criteria for response¹⁶ as a complete response with lymphoid nodules in the bone marrow); PR, partial response; PR-L, partial response with lymphocytosis.

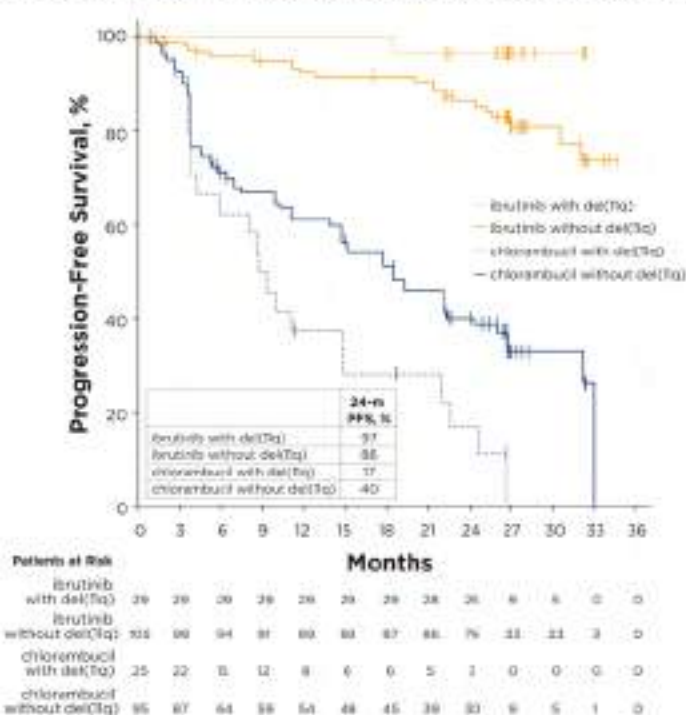
Figure 4. Safety and tolerability of ibrutinib over time. Rate of grade ≥ 3 AEs,

discontinuations due to AEs, and dose reductions over different periods of time. AE, adverse events

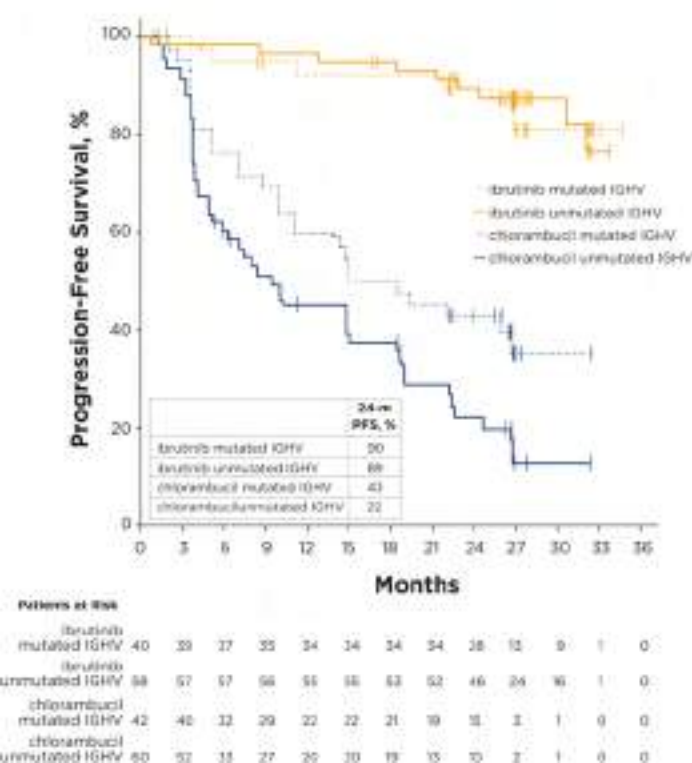
A PFS

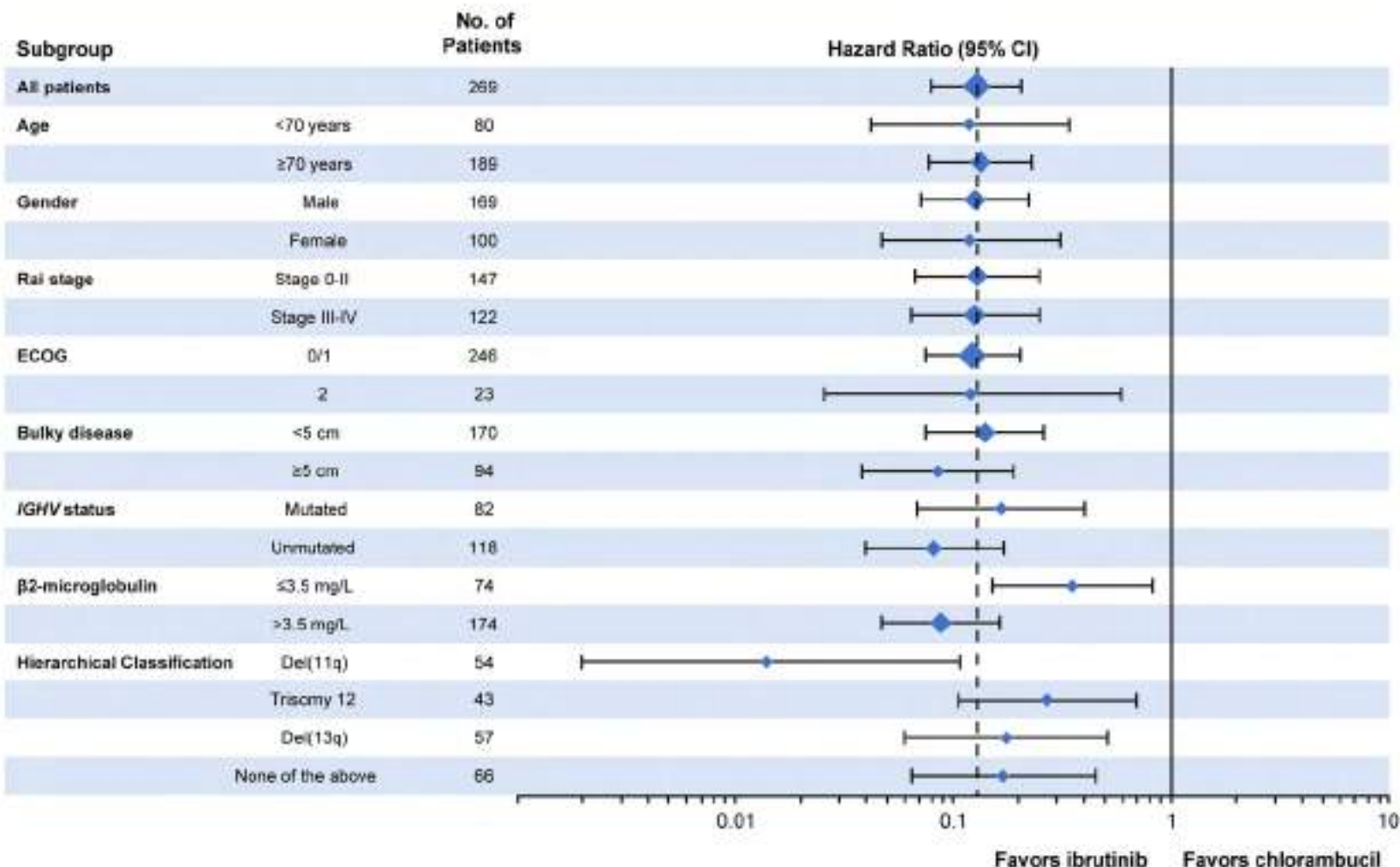


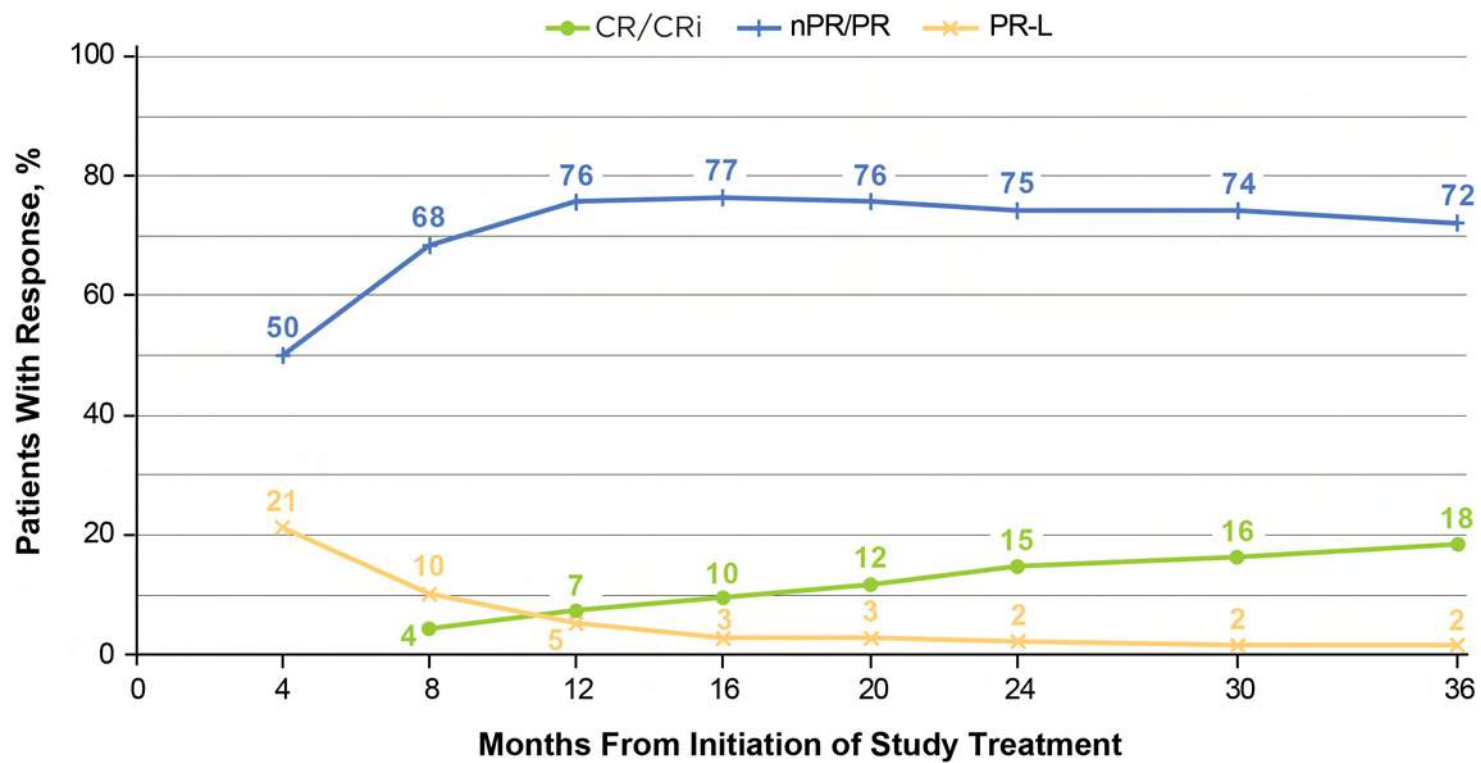
B PFS in the Presence or Absence of Del(11q)

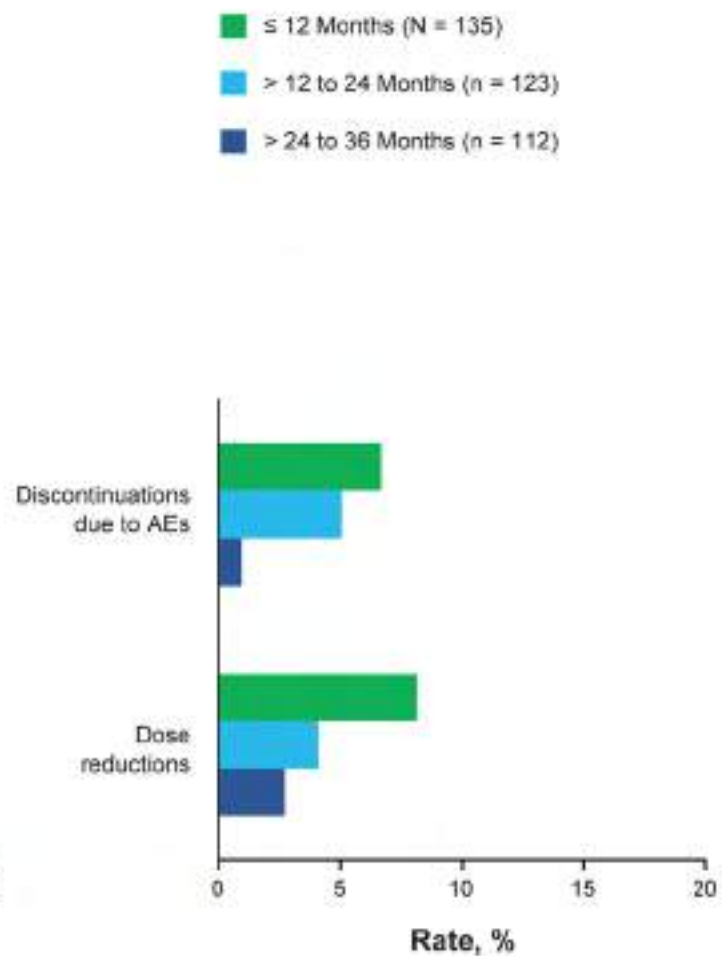
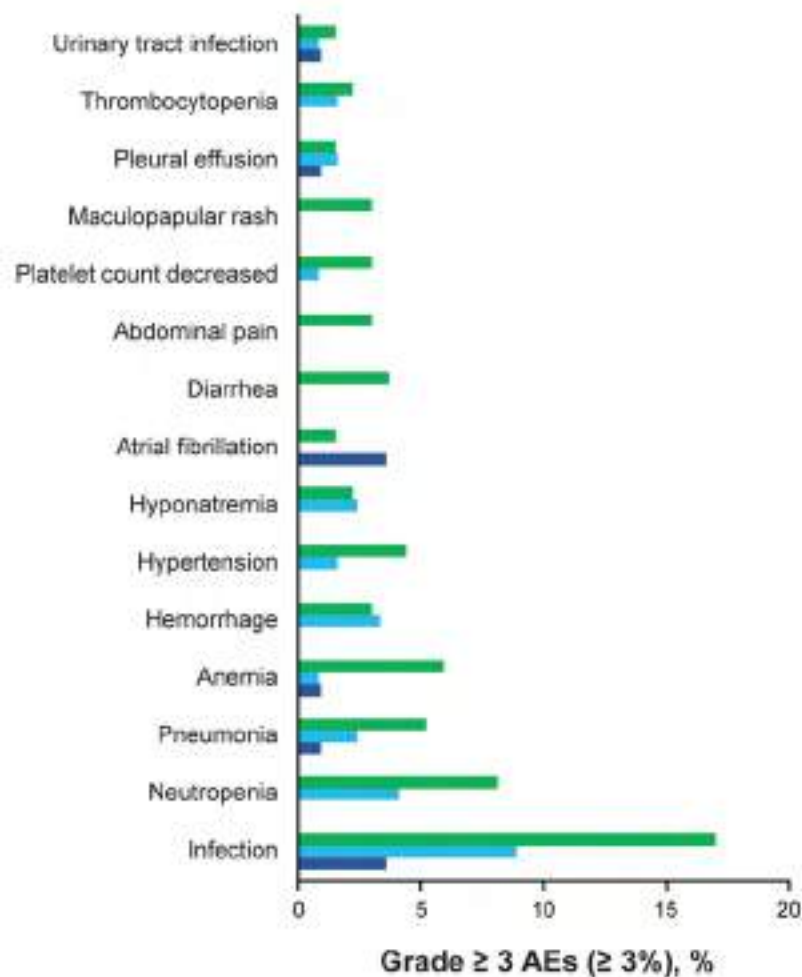


C PFS With Mutated vs Unmutated IGHV









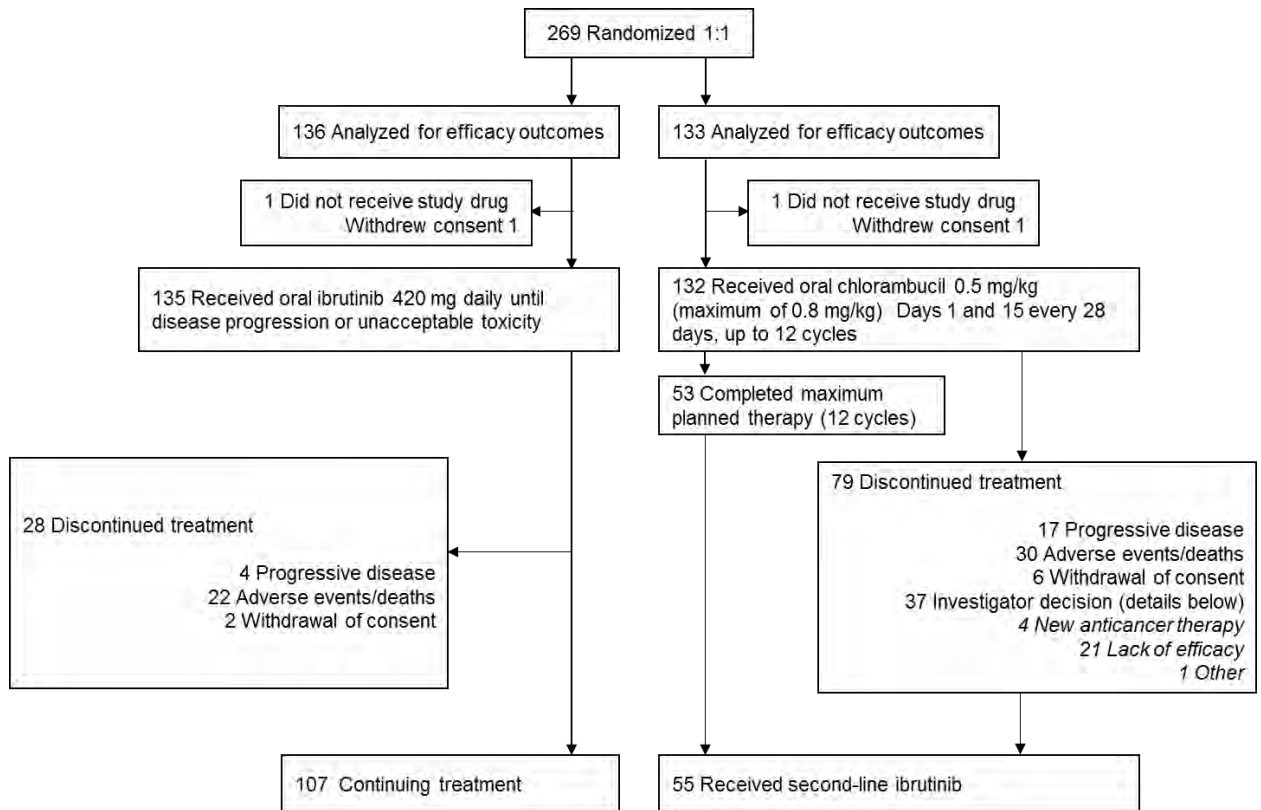
Supplementary Online Content

First-line Ibrutinib in Older Patients With Chronic Lymphocytic Leukemia: Extended Phase 3 Results From RESONATE-2

Outline

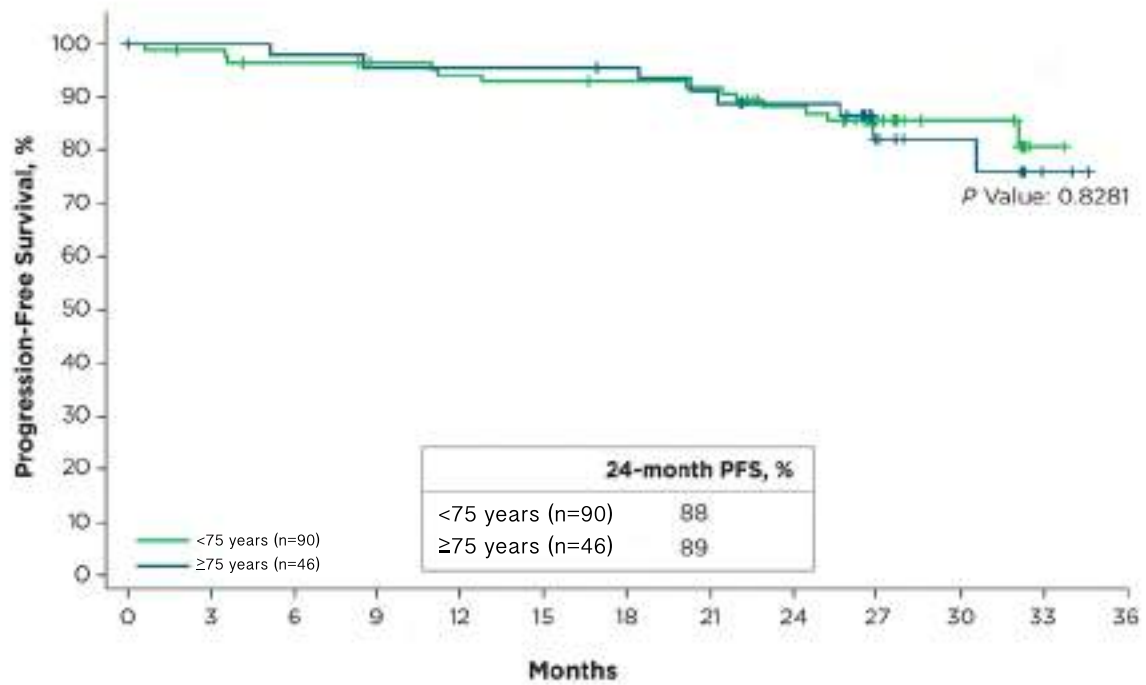
1. Figure S1: Patient flow with extended follow-up in the RESONATE-2 trial
2. Figure S2. PFS and OS for patients receiving ibrutinib by age subgroup
3. Figure S3. OS for the Intent-to-Treat Population
4. Table S1. OS Adjusted for Crossover
5. Figure S4. Reductions in Lymphadenopathy and Splenomegaly Over Time With Ibrutinib Treatment
6. Figure S5. Patient-Reported QOL Measures Over Time
7. Table S2. Most Frequent AEs ($\geq 15\%$) in Ibrutinib-Treated Patients
8. Table S3. Frequent Concomitant Medications of Clinical interest
9. Table S4. Patients Who Discontinued Ibrutinib Due to AEs and Died
10. References

1. **Figure S1.** Patient flow with extended follow-up in the RESONATE-2 trial

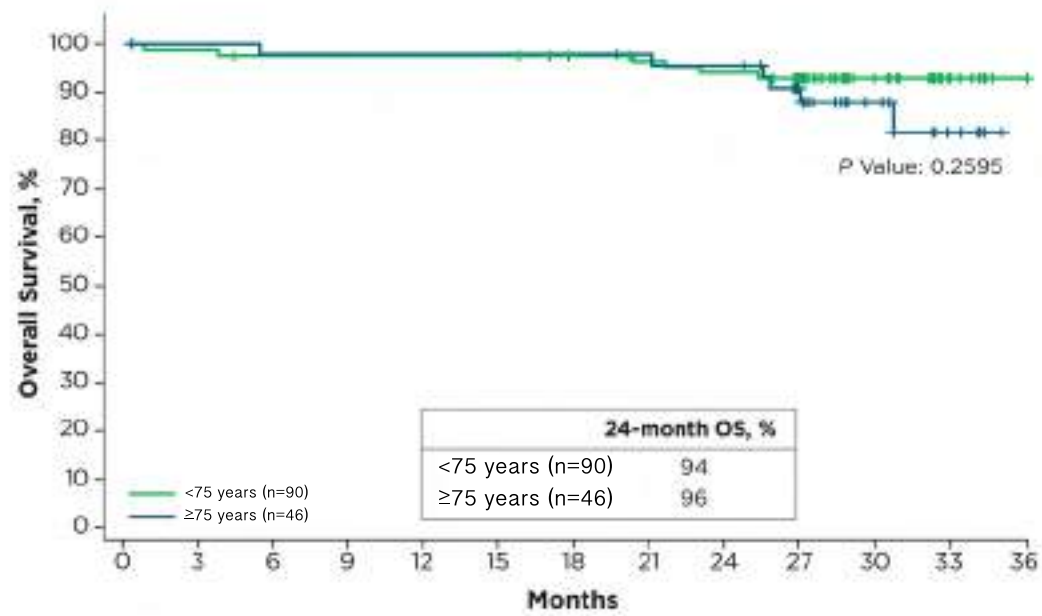


2. Figure S2. PFS and OS for patients receiving ibrutinib by age subgroup

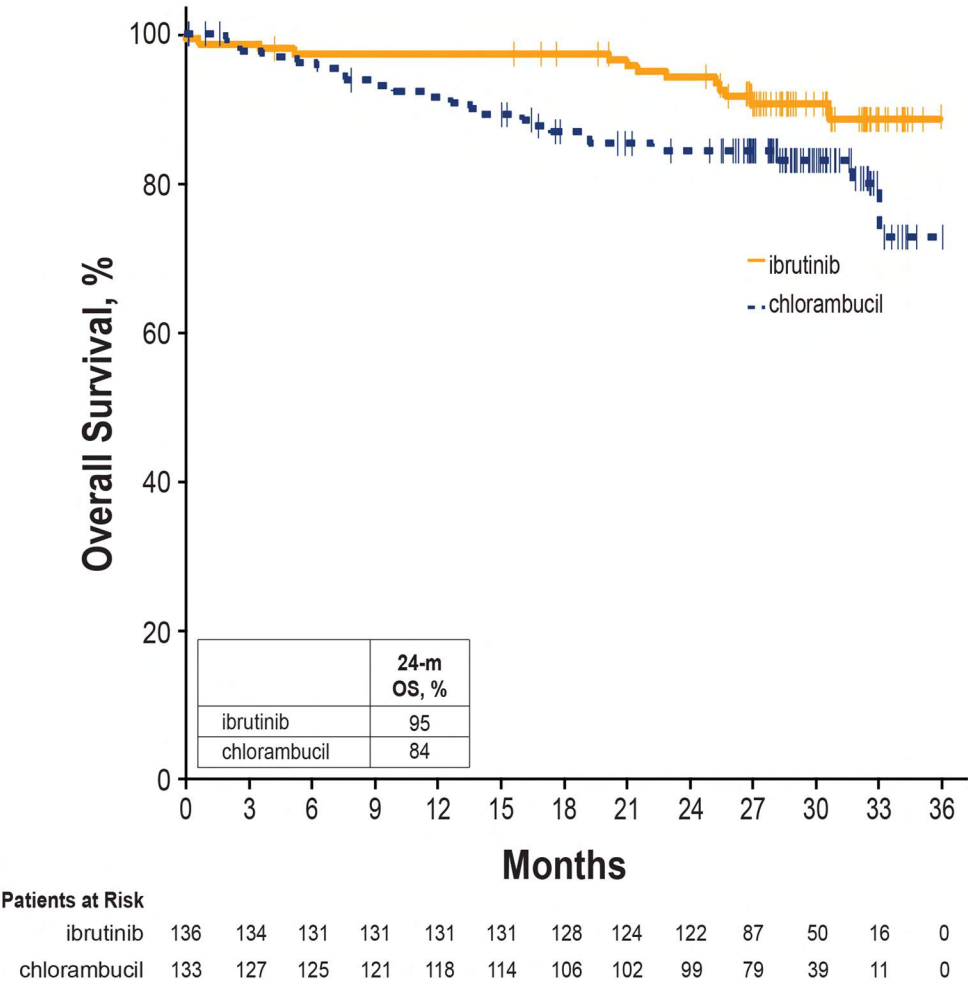
A



B



3. Figure S3. OS for the Intent-to-Treat Population



OS, overall survival.
Survival analyses from randomization until event or censored at last follow-up using the Kaplan-Meier method. Vertical ticks indicate censored patients.

4. Table S1. OS adjusted for crossover

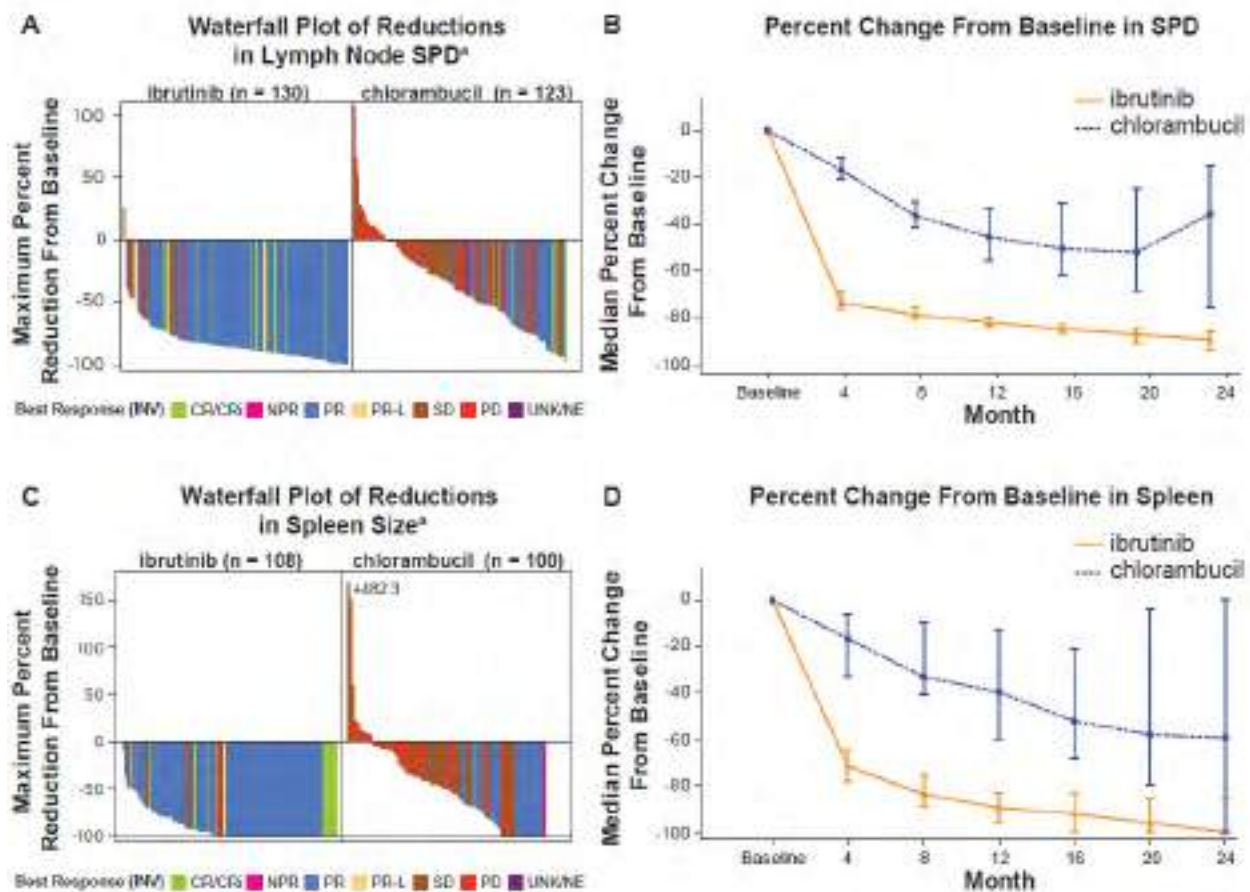
Method	Cox model		Log-rank <i>P</i> value
	HR	95% CI	
ITT	0.43	0.21-0.86	.0145
RPSFT model ^a	0.28	0.13-0.60	—
Excluding crossover patients ^b	0.31	0.15-0.66	.0013

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; RPSFT, rank-preserving structural failure time.

^a Cox model including treatment and baseline covariates to compensate for any lack of balance between treatment arms and improve precision (ECOG PS, Rai stage, age, sex, bulky disease, del11q, region, ethnicity, lactate dehydrogenase, β 2-microglobulin, creatinine clearance).

^b Analysis stratified by 2 randomization factors: ECOG PS (0/1 vs 2) and Rai stage (0/I/II vs III/IV) at baseline as reported in the interactive web response system.

5. Figure S4. Reductions in lymphadenopathy and splenomegaly over time with ibrutinib treatment.

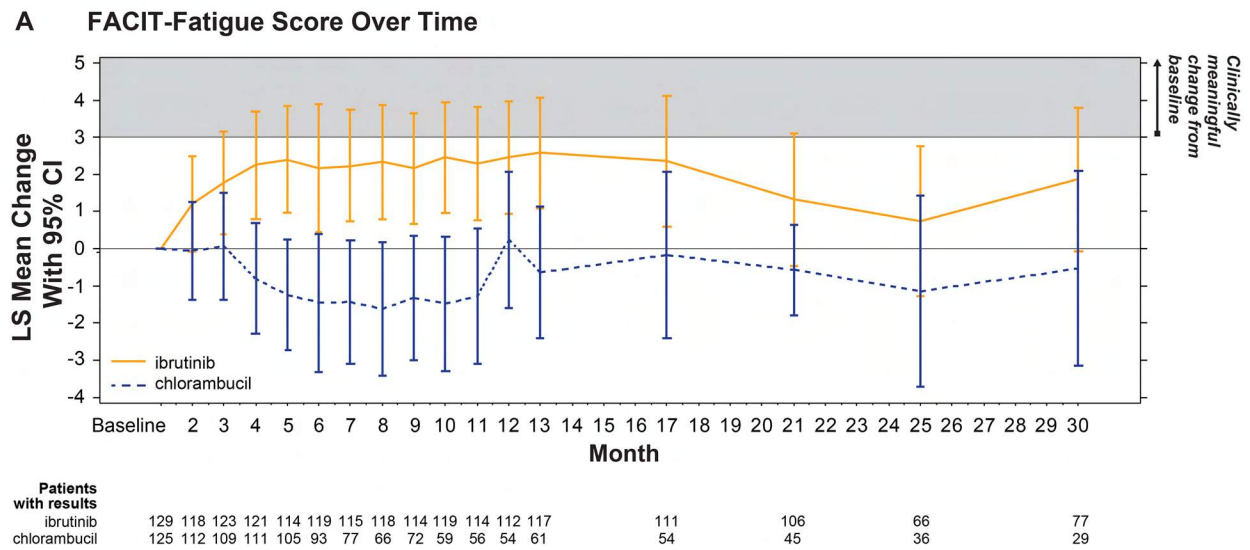


CRi, complete response with incomplete blood-count recovery; NPR, nodular partial response; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; SPD, sum of the product of perpendicular diameters of lymph nodes; UNK/NE, unknown/not evaluable.

Of patients with baseline lymphadenopathy, 95% (124/130) experienced a $\geq 50\%$ reduction in the lymph node sum of the product of longest diameter (SPD) with ibrutinib versus 40% (49/123) of those treated with chlorambucil, with complete resolution in 42% (55/130) versus 7% (9/123), respectively (A and B). Of those with baseline splenomegaly, 95% (103/108) experienced a $\geq 50\%$ reduction with ibrutinib versus 52% (52/100) with chlorambucil, with complete resolution in splenomegaly in 56% (60/108) versus 22% (22/100), respectively (C and D).

^aFor patients with measurable disease at baseline, reductions in lymphadenopathy and spleen size were measured by an Independent Review Committee at the time of primary analysis while best response was investigator assessed.

6. Figure S5. Patient-reported QOL measures over time.



CI, confidence interval; LS, least squares; QOL, quality of life.

7. Table S2. Most frequent AEs ($\geq 15\%$) in ibrutinib-treated patients

AEs, n (%)	Ibrutinib-treated patients (n=135) Median duration of treatment = 28.5 months (range, 0.7-35.9 months)					
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	61 (45)	40 (30)	16 (12)	5 (4)	0	0
Fatigue	44 (33)	29 (21)	13 (10)	2 (1)	0	0
Cough	38 (28)	30 (22)	8 (6)	0	0	0
Anemia	31 (23)	8 (6)	14 (10)	8 (6)	1 (1)	0
Nausea	31 (23)	21 (16)	9 (7)	1 (1)	0	0
Peripheral edema	29 (21)	20 (15)	7 (5)	2 (1)	0	0
Arthralgia	27 (20)	15 (11)	9 (7)	3 (2)	0	0
Pyrexia	27 (20)	17 (13)	9 (7)	0	0	1 (1)
URTI	26 (19)	7 (5)	16 (12)	3 (2)	0	0
Dry eye	25 (19)	23 (17)	2 (1)	0	0	0
Hypertension	24 (18)	4 (3)	13 (10)	7 (5)	0	0
Neutropenia	23 (17)	3 (2)	4 (3)	8 (6)	8 (6)	0
Vomiting	23 (17)	15 (11)	8 (6)	0	0	0
Constipation	22 (16)	16 (12)	5 (4)	1 (1)	0	0
Blurred vision	22 (16)	17 (13)	5 (4)	0	0	0

AE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

8. Frequent concomitant medications of clinical interest

Types of concomitant medications, n (%)	Ibrutinib (n=135) median DOT = 28.5 months (range, 0.7-35.9 months)	Chlorambucil (n=132) median DOT = 7.1 months (range, 0.5-11.7 months)
Antiplatelet agents	66 (49)	67 (51)
Acetylsalicylic acid (aspirin)	45 (33)	48 (36)
NSAIDs	35 (26)	23 (17)
Clopidogrel	8 (6)	4 (3)
Anticoagulants	28 (21)	13 (9)
LMWH	19 (14)	6 (5)
Heparin	5 (4)	1 (1)
Direct oral anticoagulants	6 (4)	6 (5)
Neutrophil growth factors	12 (9)	16 (12)
RBC transfusions	20 (15)	21 (16)
Platelet transfusions	2 (1)	3 (2)
Intravenous immunoglobulin	6 (4)	2 (2)

DOT, duration of treatment; LMWH, low-molecular-weight heparin; NSAID, nonsteroidal anti-inflammatory drug; RBC, red blood cell.

9. Table S4. Patients who discontinued ibrutinib due to AEs and died

Patient	AE leading to discontinuation	OS, months	Last dose of ibrutinib to death, days
1	Bilateral pneumonia (<i>Legionella pneumophylae</i>)	3.5	39
2	Secondary malignancy (non-small cell lung cancer)	20.2	180
3	Fever	21.5	5

AE, adverse event; OS, overall survival.

10. References

1. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425-2437.